REMARKS

STATUS OF THE CLAIMS

Claims 8, 9, 11-19, 23, 26, 28, 29, and 30 were pending in this application. Claims 8 and 30 have been amended; claims 11 and 13 have been cancelled herein. Claims 8, 9, 12, 14-19, 23, 26, 28, 29, and 30 will be pending and at issue.

SUPPORT FOR AMENDMENTS TO THE CLAIMS

Claim 8 has been amended to include elements from herein canceled claims 11 and 13. Support can be found throughout the specification as filed, e.g., original claims 11 and 13 and e.g., at page 8, lines 12-13 ("This is accomplished by culturing the cells in the presence of specific myelin antigens."); at page 11, lines 5-7 ("Cycles of restimulation and expansion were repeated weekly until the response to myelin antigens detected in proliferation assays exceeded the response to control antigens by three fold.").

Claim 30 has been amended to further clarify recitation of one embodiment of Applicant's invention, e.g., a method using attenuated T-cells prepared as described in one example of the instant application. Support can be found throughout the specification as filed, e.g., page 8 and Example 1, pages 10 and 11.

To further prosecution, Applicant has cancelled without prejudice claims 11 and 13 rendering the pending rejections moot. Applicant reserves the right to file subsequent applications claiming the canceled subject matter. In addition, the claim cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action.

The amendments to the claims therefore add no new matter and entry is respectfully requested.

REQUEST FOR EXAMINER INTERVIEW

Applicant respectfully requests an Examiner interview before issuance of an office action. In particular, Applicant is eager for suggestions regarding amendments to claim 30 to put the claim in condition for allowance.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (WRITTEN DESCRIPTION)

Claims 24, 25, and 30 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. The Examiner stated that this is a new matter rejection and that

> Applicant is advised that, in general, a specific example cannot likely support a claim comprising a generic method. In this instance, the claim begins by "obtaining a polyclonal mixture of T cells". For support Applicant cites the example wherein PBMCs from four SPMS patients are obtained by leukophoresis. Clearly the specific example cannot support the broader scope of the claim. Likewise, the establishing of autoreactive T cell lines by culture in serum-free media supplemented with gentamicin cannot support the "culturing polyclonal mixture of T cells" recited in the claim.

First, Applicant respectfully notes that claims 24 and 25 were previously canceled, rendering moot this rejection of those claims.

Turning to claim 30, the Examiner appears to be making the argument that the specification only provides written description support for a method that recites the example described, e.g., a method that recites using T-cells derived from PBMCs and prepared by the method described in Example 1. Without agreeing with the Examiner's position but rather to further prosecution and identify claim language the Examiner might consider allowable, Applicant has amended claim 30 to recite language from the example disclosed in the specification. Withdrawal of this rejection is requested.

Claims 8, 9, 11-19, 23, 26, 28, and 30 were rejected under 35 U.S.C. 112, first paragraph, as the specification allegedly does not contain a written description of the claimed invention, in that the disclosure allegedly does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

The Examiner stated that

This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) … T cells are cultured in the presence of whole bovine myelin proteins or synthetic human proteins … (Claims 8 and 30).

B) ... T cells that respond to a plurality of different myelin proteins (Claim 11).

C) ... T cells are reactive to a plurality of different myelin proteins (Claim 23).

Regarding A), Applicant cites page 8 of the specification for support.

At page 8 the specification discloses PBMCs are cultured in the presence of cow myelin proteins or synthetic complete human proteins.

Regarding B) and C), Applicant cites pages 8 and 11 of the specification for support.

At page 8 the specification discloses PBMCs are cultured in the presence specific myelin antigens. Page 11 discloses a specific example in which PBMCs and myelin antigens are employed.

Again, the Examiner appears to be making the arguments that the specification provides written description support for a method that recites only the example described., e.g., a method that recites using T-cells derived from PBMCs. Applicant respectfully disagrees with this rejection. Although the example provided by the specification describes starting with PBMCs to generate the attenuated T-cells for the claimed method, Applicant invention is not limited to the method using T-cells derived from PBMCs. At numerous points in the specification, including the claims as filed, Applicant used the terminology "T-cells" to describe the claimed invention. Additional support for can be found as follows:

Support "T-cells" not limited to PBMCs	**Location**
Another aspect of the invention is a method of treating patients with MS by vaccinating patients with attenuated T-cells.	Page 6, lines 20-21
The vaccine is comprised of attenuated T-cells that are presumed to be	Page 7, lines

Support "T-cells" not limited to PBMCs	Location
autoreactive.	20-21
Preferably, T-cells are removed from the patient by leukaphoresis.	Page 8, lines 4-5
A method of mediating an immune response, comprising the step of administering attenuated T-cells to a human	Original claim 8
The method of claim 8, wherein the T-cells are derived from autologous peripheral mononuclear cells.	Original claim 9.

Further, what is conventional or well known to one skilled in the art need not be disclosed in detail. The fact that T-cells can be derived from a variety of sources is well-known to one of skill in the art and therefore did not need to be explicitly disclosed in the specification.

Applicant respects withdrawal of this rejection as drawn to claims 8, 9, 11-19, 23, 26, and 28.

Without agreeing with the Examiner's position but rather to further prosecution, Applicant has amended claim 30 to recite more clearly the method of the example, including language regarding PBMCs. Applicant requests withdrawal of this rejection as drawn to claim 30.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (ENABLEMENT)

Claims 8, 9, 11-19, 23, 26, 28, and 30 were rejected under 35 U.S.C. 112, first paragraph as containing subject matter which was allegedly not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner stated that:

> The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level

> of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention.
>
> The instant claims encompass the use of attenuated T cells for mediating an immune response in an MS patient. Presumably, an immune response is mounted against attenuated T cells specific for MS-associated antigens, after which the newly generated response reduces the number of aberrant autoimmune T cells in the MS patient.
>
> A review of the claims reveals that, except for Claim 11, the claimed method need not employ T cells specific for, or that even respond to, any MS-associated antigens. Indeed, the method need not even limited to the use of human T cells.

Without agreeing with the Examiner's position but rather to more clearly describe Applicant's invention and to further prosecution, Applicant has amended claim 8 to recite the elements of claim 11: "wherein the T-cells are prepared by selecting and expanding T-cells that respond to a plurality of different myelin proteins." In addition, claim 8 has been amended to recite "human T-cells." As all pending claims depend on claim 8, all pending claims now include these elements.

The Examiner also stated that

> it is also noted that the method also does not require the reduction of the aberrant autoimmune response. As it is unlikely that any T cell "mediating" any sort of immune response would provide an effective treatment for MS, it is clear that practicing the breadth of the claimed invention would require undue experimentation.

Regarding claims 8, 9, 11-19, 23, 26, 28, Applicant requests further clarification from the Examiner regarding this element of the rejection. In an attempt to understand the rejection, and without agreeing with the Examiner but rather to further prosecution, Applicant has amended claim 30 to recite a specific mediation of an immune response: "wherein upon administering the attenuated T-cells the number of aberrant autoimmune T cells is reduced in said human." Applicant requests additional input from the Examiner as to whether or not this amendment would overcome the rejection.

REJECTIONS UNDER 35 U.S.C. § 102

Applicant notes that the Examiner has not cited prior art against claim 30.

Claims 8, 9, 11, 12, 14 and 15 were rejected under 35 U.S.C. 102(b) as allegedly anticipated by Stinissen et al. (1996). The Examiner stated that

> As set forth previously, Stinissen et al. teaches a method of mediating an immune response comprising administering subcutaneously irradiation-attenuated T-cells derived from autologous peripheral mononuclear cells (comprising T cells) cultured in the presence of natural or synthetic myelin proteins (see particularly page 503, T CELL VACCINATION IN MS).
>
> Applicant's arguments, filed 6/15/06 have been fully considered but they are not persuasive. Applicant argues that the amended claims recite a method not taught by the reference, in particular the reference does not employ the whole bovine myelin proteins or synthetic human myelin proteins of the claims.
>
> The instant claims recite a method of treating a human employing a product by process. In such instances, the process by which the product is made is not considered to add patentability to the method of treating. Accordingly, as the reference teaches a method of mediating an immune response comprising administering T cells, in this case cultured in the presence of human myelin proteins, the method of the reference is the method of the instant claims.

Applicant respectfully disagrees. One of skill would understand that the process taught by Stinissen, e.g., culturing T-cells in the presence of a single myelin protein, e.g., basic myelin protein (MBP), results in a product that is different from the product resulting from the method taught by Applicant, e.g., culturing T-cells in the presence of multiple myelin proteins, e.g., whole bovine myelin proteins or synthetic human myelin proteins. Stinissen does not teach culturing T-cells in the presence of multiple different myelin proteins. The product by Stinissen's process is T-cells reactive with MBP only. The product by Applicant's process is T-cells reactive with a plurality of myelin proteins. Accordingly, the method of treating a human employing the product by Stinissen's process is different from the method of treating a human employing the product of Applicant's process.

The Examiner did not reject claim 13 as anticipated by Stinissen. Applicant has amended claim 8 to recite to element of claim 13: "and wherein the administered attenuated T-cells target more than one myelin protein." In addition to the deficiencies in Stinissen mentioned above, Stinissen does not include the element of "wherein the administered attenuated T-cells target more than one myelin protein." All pending claims depend on claim 8 and therefore include this element. Accordingly, the reference does not teach each and every element of the claimed invention and cannot anticipate the claimed invention. Withdrawal of this rejection is requested.

REJECTIONS UNDER 35 U.S.C. § 103

Applicant notes that the Examiner has not cited prior art against claim 30.

Claims 16-19 were rejected under 35 U.S.C. 103(a) each as allegedly unpatentable over Stinissen et al. (1996). The Examiner stated that

> The reference differs from the claimed invention only in that it does not teach the optimization of the claimed method as set forth in dependent Claims 16-19. For example, the choice of dosage (Claim 17), and timing (Claim 16), would have fallen well within the purview of the skilled artisan at the time of the invention. Regarding the increasing of the dosages as set forth in Claims 18 and 19, one of ordinary skill in the art at the time the invention was made would have been well aware of the concept of increasing dosage if no response is obtained up to the point of efficacy or adverse reaction. These limitations do not render the claimed method patentably distinct.

As described above, Applicant has amended claim 8 to recite the element "and wherein the administered attenuated T-cells target more than one myelin protein." Claims 16-19 depend on claim 8 and include this element. The combination of prior art cited by the Examiner does not include this element and Applicant respectfully requests withdrawal of this rejection.

Claim 13 stands rejected under 35 U.S.C. 103(a) each as allegedly unpatentable over Stinissen et al. (1996) in view of Correale et al (1995).

The Examiner stated that

> As set forth previously, Stinissen et al. has been discussed above. The reference further teaches that MBP is not the only autoantigen candidate in MS. The reference teaches that additional antigens, including PLP,

MAG, and MOG might also be the targets of autoreactive T cells (see particularly page 501, column 1, second full paragraph).

The reference differs from the claimed invention only in that it does not teach the use of attenuated T cells that target more than one myelin protein.

Correale et al. extends the teachings of Stinissen et al. regarding. additional MS autoantigens. The reference teaches that as MS develops, myelin breakdown exposes additional myelin antigens (besides MBP) to autoreactive T cells, thus, broadening the autoimmune response (see particularly page 1375, last paragraph - page 1376, first paragraph.

From the teachings of the references it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to perform the method of administering attenuated T cells, as taught by Stinissen et al., employing attenuated T cells autoreactive to multiple myelin antigens. One of ordinary skill in the art at the time the invention was made would have been motivated to employ attenuated T cells autoreactive to multiple myelin antigens given the teachings of Stinissen et al. that MBP is not the only autoantigen candidate in MS and extended by Correale et al. that as MS develops, myelin breakdown exposes additional myelin antigens (besides MBP) to autoreactive T cells, thus broadening the autoimmune response.

Applicant has canceled claim 13, rendering moot this rejection. Claim 8 has been amended to recite the element of claim 13: "wherein the administered attenuated T-cells target more than one myelin protein." In addition, claim 8 has been amended to also recite the element from cancelled claim 11: "and prepared by selecting and expanding human T-cells that respond to a plurality of different myelin proteins." Claim 11 was not rejected as obvious over Stinissen and Correale.

The combination of Stinissen and Correale do not render any of the pending claims obvious because the combination of art does not include the element of "prepared by selecting and expanding human T-cells that respond to a plurality of different myelin proteins." Indeed, Stinissen teaches away from the method as claimed and described by Applicant when Stinissen described the necessity of cloning the T-cells, e.g., generating highly purified T-cell clones. As described on page 503, middle of the first paragraph:

> This T cell cloning method is very critical in the vaccine preparation since only highly purified T cell clones can be expanded to the number of cells need for vaccination. (Emphasis added)

A single highly purified T-cell clone, as taught by Stinissen, by definition cannot include T-cells that respond to a plurality of different proteins and prepared by selecting and expanding human T-cells that respond to a plurality of different myelin proteins. One of skill in the art would not be motivated to combine the method taught by Stinissen with the additional MS myelin antigens taught by Correale because one of skill would read Stinissen and have no expectation of success in generating a vaccine using T-cells that are not cloned..

Further support for this argument can be found in a subsequent publication by the same group that authored Stinissen, "Van der AA" (Van der AA et al (2003) T cell vaccination in multiple sclerosis patients with autologous CSF-derived activated T cells: results from a pilot study. Clin Exp Immunol 131:155-168, submitted concurrently with an IDS). First, the authors describe the "TCV protocol" using MBP specific clonal T cells as described in Stinissen. Then, on page 156, first full paragraph of Van der AA, the authors describe how generating a T-cell vaccine specific for more than one myelin antigen and using the techniques described in Stinissen is "almost impossible:"

> Increasing evidence indicates that T cells recognizing other myelin component may also contribute to the disease process in MS. Experiments in EAE and studies in human T cell reactivity demonstrated that PLP and MOG may play an important role as candidate myelin antigens in the autoimmune mediated demyelination. Incorporating T cell populations specific for these autoantigens in the vaccines may improve the effectiveness of the current TCV protocol. However, technically it is almost impossible to generate T cell clones specific for three different myelin antigens with the current protocol design. (Emphasis added)

Given that Stinissen describes the critical need for T-cell cloning in generating a T cell vaccine, and that a subsequent publication by the same group describes the impossibility of a T cell vaccine directed to multiple myelin antigens using the clonal method, one of skill would have had no expectation of success when combing Stinissen and Correale. The prima facie case of obviousness in not made, and withdrawal of this rejection is respectfully requested.

CONCLUSION

Withdrawal of the pending rejections and reconsideration of the claims are respectfully requested, and a notice of allowance is earnestly solicited. If the Examiner has any questions concerning this Response, the Examiner is invited to telephone Applicant's representative at (415) 875-2316.

Respectfully submitted,
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Dated: February 7, 2007

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